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# DESCRIPTION

## FIELD OF THE INVENTION

**[0001]** The present invention relates to compounds for use in treating disorders associated with α-adrenergic receptor modulation, such as pain.

## BACKGROUND OF THE INVENTION

**[0002]** Clinical pain encompasses nociceptive and neuropathic pain. Each type of pain is characterized by hypersensitivity at the site of damage and in adjacent normal tissue. While nociceptive pain usually is limited in duration and responds well to available opioid therapy, neuropathic pain can persist long after the initiating event has healed, as is evident, for example, in the "ghost pain" that often follows amputation. Chronic pain syndromes such as chronic neuropathic pain are triggered by any of a variety of insults, including surgery, compression injury or trauma, infectious agent, toxic drug, inflammatory disorder, or a metabolic disease such as diabetes or ischemia.

**[0003]** Unfortunately, chronic pain such as chronic neuropathic pain generally is resistant to available drug therapy. Furthermore, current therapies have serious side-effects such as cognitive changes, sedation, nausea and, in the case of narcotic drugs, addiction. Many patients suffering from neuropathic and other chronic pain are elderly or have medical conditions that limit their tolerance to the side-effects associated with available analgesic therapy. The inadequacy of current therapy in relieving neuropathic pain without producing intolerable side-effects often is manifest in the depression and suicidal tendency of chronic pain sufferers.

**[0004]** As alternatives to current analgesics, $\alpha_2$ adrenergic agonists, which are devoid of respiratory depressant effects and addictive potential are being developed. Such drugs are useful analgesic agents when administered spinally. However, undesirable pharmacological properties of α-adrenergic agonists, specifically sedation and hypotension, limit the utility of these drugs when administered orally or by other peripheral routes. Thus, there is a need for effective analgesic agents that can be administered by oral or other peripheral routes and that lack undesirable side-effects such as sedation and hypotension. The present invention satisfies this need and provides related advantages as well.

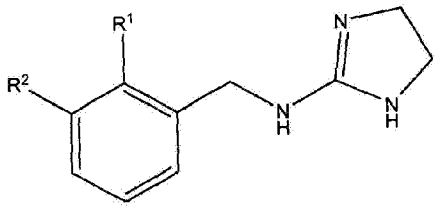
**[0005]** Also provided herein are new therapies for chronic pain sufferers, who, until now, have faced a lifetime of daily medication to control their pain. Unfortunately, available treatments for chronic neuropathic pain, such as tricyclic antidepressants, anti-seizure drugs and local anesthetic injections, only alleviate symptoms temporarily and to varying degrees. No available treatment reverses the sensitized pain state or cures pain such as neuropathic pain. Effective

drugs that can be administered, for example, once or several times a month and that maintain analgesic activity for several weeks or months, are presently not available. Thus, there is a need for novel methods of providing long-term relief from chronic pain. The present invention satisfies this need and also provides related advantages.

**[0006]** WO 2009/052075, which represents prior art under Article 54(3) EPC, discloses $\alpha_{2B}$ adrenergic agonists for use in treating motor disorders. The $\alpha_{2B}$ agonists include N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine.

## SUMMARY OF THE INVENTION

**[0007]** An aspect of the present invention is a compound represented by the following formula, or a pharmaceutically acceptable salt or tautomer thereof, for use in a method of treating a condition or disease in a mammal selected from hypertension, congestive heart failure, asthma, depression, glaucoma, elevated intraocular pressure, ischemic neuropathy, optic neuropathy, pain, a retinal degenerative condition, stroke, a cognitive deficit, a neuropsychiatric condition, drug dependence, drug addiction, withdrawal symptoms, obsessive compulsive disorder, obesity, insulin resistance, a stress-related condition, diarrhea, diuresis, nasal congestion, attention deficit disorder, psychosis, anxiety, autoimmune disease, Crohn's disease, gastritis, and a neurodegenerative disease:




wherein $R^1$ and $R^2$ are each independently selected from halogen and $C_{1-4}$ halogenated alkyl.

**[0008]** In one embodiment, the condition or disease is pain.

**[0009]** In one embodiment, the compound is N-(2-chloro-3-fluoro-benzyl)-4,5-dihydro-1H-imidazol-2-amine. In another embodiment, the compound is N-(2-fluoro-3-trifluoromethyl-benzyl)-4,5-dihydro-1H-imidazol-2-amine. In another embodiment, the compound is N-(3-chloro-2-fluoro-benzyl)-4,5-dihydro-1H-imidazol-2-amine. In another embodiment, the compound is N-(2,3-dichloro-benzyl)-4,5-dihydro-1H-imidazol-2-amine. In another embodiment, the compound is N-(2-chloro-3-bromo-benzyl)-4,5-dihydro-1H-imidazol-2-amine. In another embodiment, the compound is N-(2-bromo-3-chloro-benzyl)-4,5-dihydro-1H-imidazol-2-amine.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0010]**

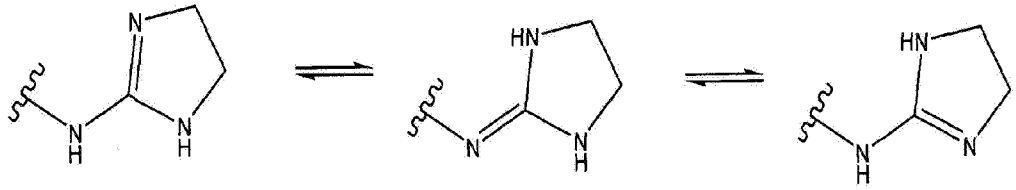
Fig. 1 depicts the peripheral analgesic effects of a single oral dose of N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine in Chung model rats at 30 µg/kg, 100 µg/kg or 300 µg/kg.

Fig. 2 depicts sedative effects (total activity counts) 30 minutes post intraperitoneal injection of 1 mg/kg and 10 mg/kg doses of N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine.

## DEFINITION OF TERMS

**[0011]** Halogen: As used herein, "halogen" refers to a substituent found in column VIIA of the periodic table of elements, including fluorine, chlorine, bromine, and iodine.

**[0012]** Tautomer: As used herein, "tautomer" refers to the migration of protons between adjacent single and double bonds. The tautomerization process is reversible. Compounds described herein can undergo the following tautomerization:




## DETAILED DESCRIPTION OF THE INVENTION

**[0013]** $\alpha_2$ adrenergic receptors have been characterized by molecular and pharmaceutical methods; the methods including $\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$, $\alpha_{2A}$, $\alpha_{2B}$ and $\alpha_{2C}$ subtypes. Activation of these α-receptors can evoke physiological responses. Adrenergic modulators described herein activate one or both of the $\alpha_{2B}$ and/or $\alpha_{2C}$ receptors and have useful therapeutic actions.

**[0014]** The compounds of the invention are useful for the treatment of the conditions and diseases recited above, which are alleviated by $\alpha_{2B}$ and/or $\alpha_{2C}$ activation.

**[0015]** Applicants have discovered that the compounds of the invention act as highly effective analgesics, particularly in chronic pain models, with minimal undesirable side effects, such as sedation and cardiovascular depression, commonly seen with agonists of $\alpha_{2B}$ and $\alpha_{2C}$ receptors.

**[0016]** The compounds may be administered at pharmaceutically effective dosages. Such dosages are normally the minimum dose necessary to achieve the desired therapeutic effect;

in the treatment of chromic pain, this amount would be roughly that necessary to reduce the discomfort caused by the pain to tolerable levels. Generally, such doses will be in the range 1-1000 mg/day; more preferably in the range 10 to 500 mg/day. However, the actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the pain, the age and weight of the patient, the patient's general physical condition, the cause of the pain, and the route of administration.

**[0017]** The compounds are useful in the treatment of pain in a mammal, particularly a human being. Preferably, the patient will be given a compound of the invention orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like. However, other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without limitation, transdermal, parenteral, subcutaneous, intranasal, intrathecal, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

**[0018]** The compounds of the invention can be included in therapeutic compositions together with a pharmaceutically acceptable excipient. Such an excipient may be a carrier or a diluent; this is usually mixed with the active compound, or permitted to dilute or enclose the active compound. If a diluent, the carrier may be a solid, semi-solid, or liquid material that acts as an excipient or vehicle for the active compound. The formulations may also include wetting agents, emulsifying agents, preserving agents, sweetening agents, and/or flavoring agents. If used as in an ophthalmic or infusion format, the formulation will usually contain one or more salts to influence the osmotic pressure of the formulation.

**[0019]** The compounds of the invention are effective in the treatment of pain, particularly chronic pain. As indicated above, the compounds will usually be formulated in a form consistent with the desired mode of delivery.

**[0020]** The mammal can be any mammal capable of experiencing pain, for example, a human or other mammal such as a primate, horse, cow, dog or cat.

**[0021]** The compounds of the invention can be used to treat both acute and chronic pain, and, as non-limiting examples, pain which is neuropathic, visceral or inflammatory in origin. In particular embodiments, the pain is selected from neuropathic pain; visceral pain; post-operative pain; pain resulting from cancer or cancer treatment; and inflammatory pain.

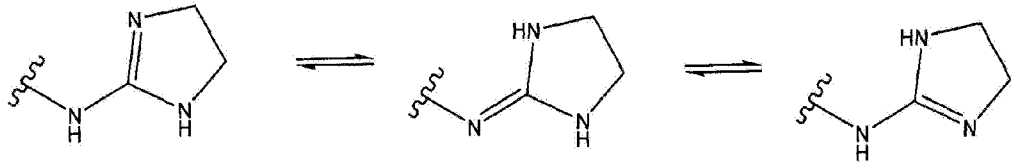
**[0022]** The term "pain" encompasses both acute and chronic pain. As used herein, the term "acute pain" means immediate, generally high threshold, pain brought about by injury such as a cut, crush, burn, or by chemical stimulation such as that experienced upon exposure to capsaicin, the active ingredient in chili peppers. The term "chronic pain," as used herein, means pain other than acute pain and includes, without limitation, neuropathic pain, visceral pain, inflammatory pain, headache pain, muscle pain and referred pain. It is understood that

chronic pain is of relatively long duration, for example, several years and can be continuous or intermittent.

**[0023]** Unless otherwise indicated, reference to a compound should be construed broadly to include compounds, pharmaceutically acceptable salts, tautomers, alternate solid forms, non-covalent complexes, and combinations thereof, of a chemical entity of a depicted structure or chemical name.

**[0024]** A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A pharmaceutically acceptable salt also refers to any salt which may form *in vivo* as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acid/carboxylate), one or more protonated basic groups (e.g. amine/ammonium), or both (e.g. zwitterions).

**[0025]** Tautomers are isomers that are in rapid equilibrium with one another. For example, tautomers may be related by transfer of a proton, hydrogen atom, or hydride ion. Not intended to be limited by the above described compounds, various tautomers of the above compounds may be possible. For example, not intended as a limitation, tautomers are possible between the 4,5-dihydrooxazole and the adjacent nitrogen as shown below.




**[0026]** Other tautomers are possible when the compound includes, for example but not limited to, enol, keto, lactamin, amide, imidic acid, amine, and imine groups. Tautomers will generally reach an equilibrium state wherein the double bond is resonantly shared between the two bond lengths.

**[0027]** Unless stereochemistry is explicitly and unambiguously depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

**[0028]** Alternate solid forms are different solid forms than those that may result from practicing the procedures described herein. For example, alternate solid forms may be polymorphs, different kinds of amorphous solid forms, glasses, and the like.

**[0029]** Non-covalent complexes are complexes that may form between the compound and one or more additional chemical species that do not involve a covalent bonding interaction between the compound and the additional chemical species. They may or may not have a specific ratio between the compound and the additional chemical species. Examples might

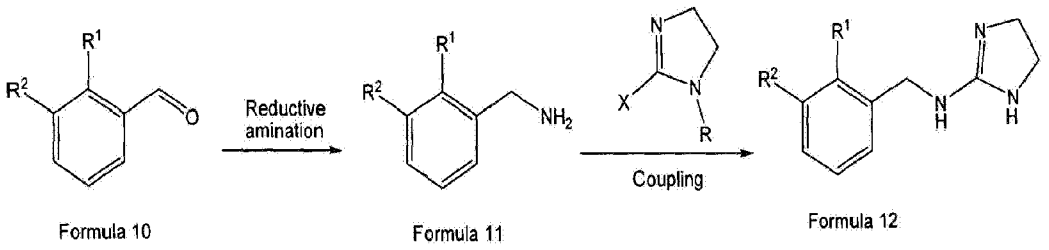
include solvates, hydrates, charge transfer complexes, and the like.

**[0030]** The following examples provide synthesis methods for forming compounds described herein. One skilled in the art will appreciate that these examples can enable a skilled artisan to synthesize the compounds described herein.

**Example 1**

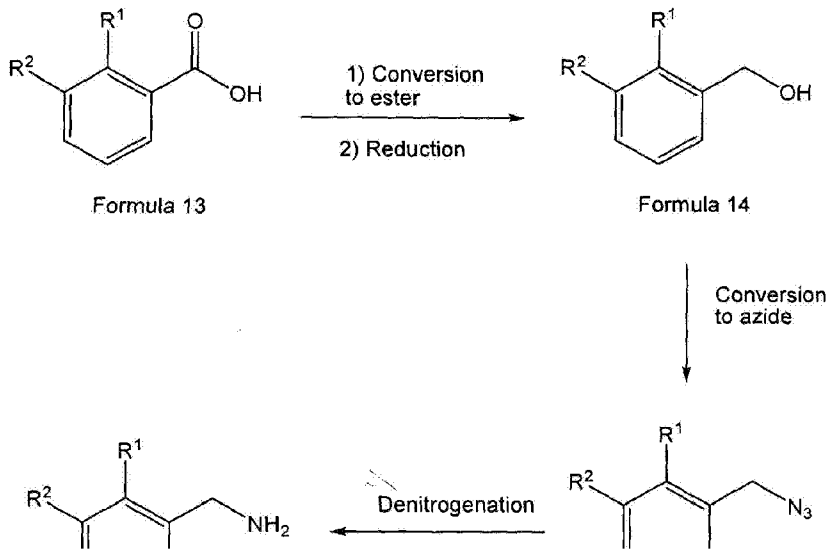
**Generic Reaction 1**

**[0031]**
**Scheme A**




**[0032]** In scheme A above, Formula 11 was either commercially available or synthesized by different reductive amination methods from Formula 10. One of those methods was published by David J. H. et al (J. Org. Chem. 48: 289-294 (1983)). The key step was the coupling for Formula 11 with imidazoline which had an appropriate leaving group on the second position to give Formula 12. The leaving group may be methylthiol (R=(O)COMe) or sulfuric acid (R=H). There are also other known coupling procedures known by those skilled in the art or by modifications of known procedures known by those skilled in the art.

**Scheme B**



Formula 11

Formula 15

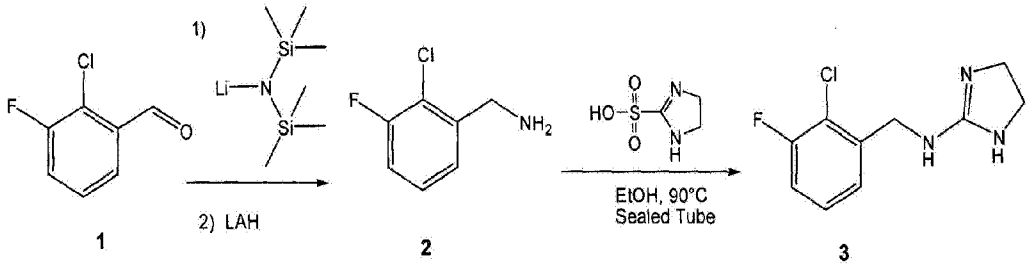
**[0033]** In Scheme B, another method is depicted to synthesize Formula 11 from substituted benzoic acid, substituted ester or substituted benzyl alcohol, all of which are commercially available. Formula 13 was converted to an ester which can be reduced to Formula 14 with lithium aluminum hydride (LAH) or borane as reagents. Conversion of the alcohol, Formula 14, to the azide, Formula 15, may be accomplished by methods such as Mitsunobu reaction with diphenylphosphoryl azide in one step, or converting alcohol to a good leaving group which can be replaced with azide anion. Denitrogenation of azide to amine was carried out with a phosphine such as triphenyl phosphine. Subsequent basic hydrolysis liberated the intermediate to amine.

**[0034]** The compounds described herein may also be synthesized by other methods known by those skilled in the art.

**Example 2**

**Synthesis of N-(2-chloro-3-fluoro-benzyl)-4,5-dihydro-1H-imidazol-2-amine**

**[0035]**



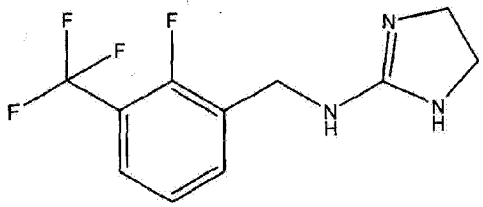

**[0036]** To a 7.08 mmol solution of 2-chloro-3-fluorobenzaldehyde **1** (1.00 g, commercially available from 3B Medical Systems, Inc.) in 8.0 mL of tetrahydrofuran (THF) was added 8.50 mL of 1.0M lithium bis(trimethylsilyl)-amide via syringe at 0°C. The resulting solution was stirred at 0°C for 3 hours. 8.50 mL of 1.0M LAH was added via syringe. Three hours later, the reaction mixture was carefully poured onto crushed ice. Ammonium chloride (aq) and Rochelle's salt (aq) were added to this mixture. The aqueous layer was extracted three times with 200 mL of chloroform/isopropanol (3:1). The pooled organic layer was dried over magnesium sulfate. The mixture was filtered, and the solvents were removed under vacuum to give (2-cholor-3-fluorophenyl)methanamine **2**. The weight of the product was 0.92 g.

**[0037]** A mixture of 0.92 g of (2-cholor-3-fluorophenyl)methanamine **2** and 0.790 g of 4,5-

dihydro-1H-imidazole-2-sulfonic acid (commercially available from Astatech) in 10.0 mL of ethanol was heated in a sealed tube to 90°C for 16 hours. Then, the reaction mixture was cooled to room temperature. Next, the ethanol was removed under vacuum. The remaining residue was basified with aqueous sodium bicarbonate solution and the pH was adjusted to about 10 with 2M sodium hydroxide. The aqueous layer was extracted three times with 100 mL of chloroform/isopropanol (3:1). The pooled organic layer was dried over magnesium sulfate and the mixture was then filtered. Amino-modified silica gel was added to the filtrate and the solvents were removed under vacuum. Purification by chromatorography on amino-modified silica gel (3.5% methanol in dichloromethane afforded 0.575 g of N-(2-chloro-3-fluoro-benzyl)-4,5-dihydro-1H-imidazol-2-amine **3** as a yellow solid.

**[0038]** $^1$H NMR (300 MHz, $CD_3OD$): δ 7.32-7.21 (m, 2H), 7.15-7.09 (m, 1H), 4.42 (s, 2H), 3.48 (s, 4H).

**[0039]** The following compounds can also be prepared according to Example 2.

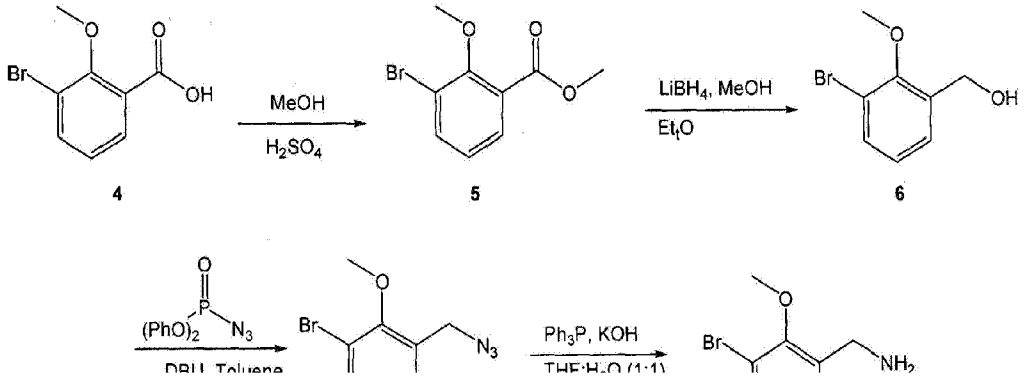


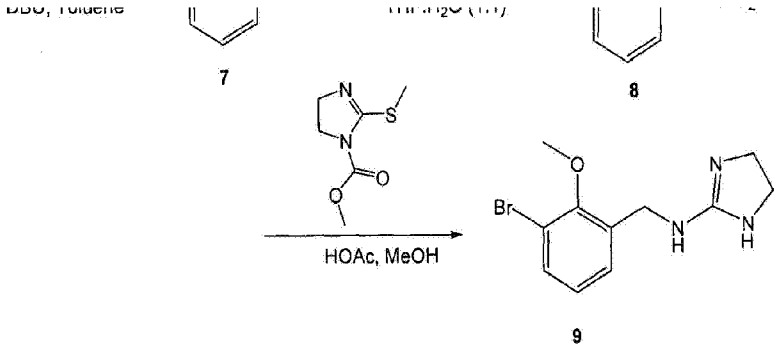
**[0040]** N-(2-fluoro-3-trifluoromethyl-benzyl)-4,5-dihydro-1H-imidazol-2-amine: $^1$H NMR (300 MHz, $CD_3OD$): δ= 7.66 (t, J=7.5 Hz, 1H), 7.57 (q, J=7.5 Hz, 1H), 7.30 (t, J=7.5 Hz, 1 H), 4.42 (s, 2H), 3.50 (s, 4H).

**Example 3**

**Synthesis of N-(3-bromo-2-methoxy-benzyl)-4,5-dihydro-1H-imidazol-2-amine (reference compound)**

**[0041]**






**[0042]** 5.0 mL of sulfuric acid ($H_2SO_4$) was slowly added to a solution of 5.0 g of 3-bromo-2-methoxy-benzoic acid **4** in 100 mL of methanol (MeOH). The resulting solution was heated to reflux overnight. The solution was cooled to room temperature and quenched with sodium bicarbonate to pH 7. The aqueous layer was extracted several times with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulphate. The resulting mixture was filtered. The solvents were evaporated under reduced pressure to afford 5.3 g of 3-bromo-2-methoxy-benzoic acid methyl ester **5**.

**[0043]** 2.4 g of lithium borohydride ($LiBH_4$) was added to a solution of 5.3 g of 3-bromo-2-methoxy-benzoic acid methyl ester **5** in 200 mL of ether ($Et_2O$) at 0°C. After stirring for 5 minutes, 5 mL of methanol was added. The reaction mixture was warmed to room temperature and kept there for 2.5 hours. Thereafter, 2.4 g more of lithium borohydride was added. The reaction mixture was quenched with aluminum chloride. After standard aqueous work up, and silica gel column purification (hexane/ethyl acetate 2:1), 4.0 g of 3-bromo-2-methoxy-phenyl-methanol **6** was obtained.

**[0044]** 6.00 g of diphenyl phosphorazidate and 4.1 g of 1,8-diazabicyclo[5.4.0] undec-7-ene were added to 4.0 g of 3-bromo-2-methoxy-phenyl-methanol **6** in 100 mL of toluene at 0°C. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate/THF. The pooled organic extracts were washed with brine and dried over magnesium sulfate. The mixture was filtered. The solvents were removed under vacuum. The residue was purified by chromatography on silica gel to give 1-azidomethyl-3-bromo-2-methoxy-benzene **7**.

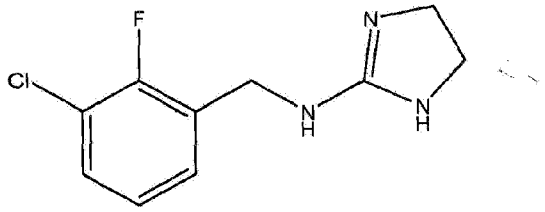
**[0045]** 1.1 g of potassium hydroxide (KOH) and 5.8 g of triphenyl phophine ($Ph_3P$) were added to a solution of 1-azidomethyl-3-bromo-2-methoxy-benzene **7** in 100 mL of THF and 10 mL of water. The mixture was stirred overnight at room temperature. The mixture was quenched with aqueous concentrated hydrochloride. After standard acid/base aqueous work up, 3.9 g of crude 3-bromo-2-methoxy-benzylamine **8** was obtained (after two steps).

**[0046]** 10 mL of acetic acid (HOAc) was added to a solution of 3.9 g of 3-bromo-2-methoxy-benzylamine **8** and 3.1 g of methyl 2-(methylthio)-4,5-hihydro-1H-imidazole-1-carboxylate in 100 mL of methanol. The resulting solution was heated to a gentle reflux and refluxed

overnight. The solution was cooled to room temperature, quenched with sodium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate. The mixture was then filtered. The solvents were removed under vacuum. The remaining residue was purified by chromatography on silica gel (10% saturated ammonia methanol in dichloromethane) to give (3-bromo-2-methoxy-benzyl-4,5-dihydro-1H-imidazol-2-yl)-amine **9**.

**[0047]** $^1$H NMR (300 MHz, $CD_3OD$): δ= 7.51 (d, J=3 Hz, 1H), 7.25-7.29 (m, 1H), 6.80 (d, J=9 Hz, 1H), 4.46 (s, 2H), 3.84 (s, 4H), 3.63 (s, 3H).

**[0048]** The following compound of the invention can be prepared using the method of Example 3.

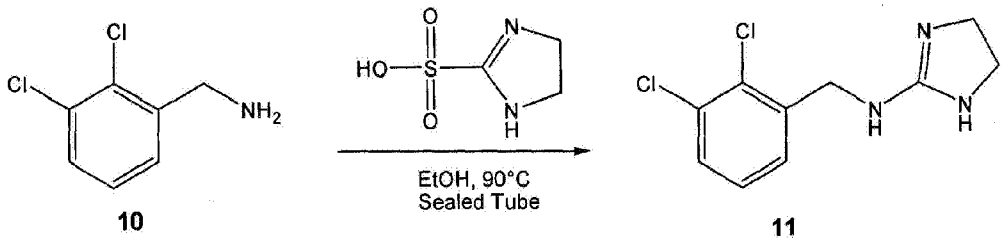



**[0049]** N-(3-chloro-2-fluoro-benzyl)-4,5-dihydro-1H-imidazol-2-amine: $^1$H NMR (300 MHz, $CD_3OD$): δ= 7.40-7.31 (m, 2H), 7.16-67.10 (m, 1 H), 4.42 (s, 2H), 3.56 (s, 4H).

**Example 4**

**Synthesis of N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine**

**[0050]**




**10** **11**

**[0051]** A mixture of 5.32 g of (2,3-dichlorophenyl)methanamine **10** and 4.56 g of 4,5-hihydro-1H-imidazole-2-sulfonic acid are mixed in 40.0 mL ethanol (EtOH) and heated in a sealed tube at 90 °C for 16 hours. Then, the reaction mixture was cooled to room temperature. Next, the ethanol was removed under vacuum. The remaining residue was basified with aqueous sodium bicarbonate solution and the pH was adjusted to about 10 with 2M sodium hydroxide. The aqueous layer was extracted three times with 400 mL of chloroform/isopropanol (3:1). The

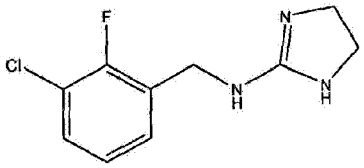
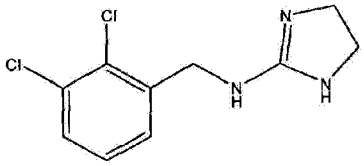
pooled organic layer was dried over magnesium sulfate and the mixture was then filtered. The filtrate was added to amino-modified silica gel (4-5% methanol in dichloromethane) and afforded 3.99 g of Compound **11** as a yellow solid.

**[0052]** $^1$H NMR (300 MHz, $CD_3OD$): δ 7.43 (dd, J=7.8, 1.8 Hz, 1H, 7.37-7.33 m, 1H), 7.26 (t, J=7.8 Hz, 1H), 4.43 (s, 2H), 3.51 (s, 4H)

**Example 5**

**Biological Intrinsic Activity Data**

**[0053]** Certain compounds described herein were tested for α-adrenergic activity using the Receptor Selection and Amplification Technology (RSAT) assay (Messier et al., 1995, Pharmacol. Toxicol. 76, pp. 308-311). Cells expressing each of the $\alpha_2$ adrenergic receptors alone were incubated with the various compounds and a receptor-mediated growth response was measured. The compound's activity is expressed as its relative efficacy compared to standard full agonist (see Table 1 below). The compounds described herein activate $\alpha_{2B}$ and/or $\alpha_{2C}$ receptors.

| Compound | $\alpha_{1A}$ | $\alpha_{2B}$ | $\delta_{2C}$ |
|---|---|---|---|
|  | 587 (1.01) | 33 (1.11) | 484 (0.60) |
|  | 282 (1.10) | 14.0 (0.94) | 46.8 (0.48) |

**Example 6**

**Biological Intrinsic Activity Data**

**[0054]** Various concentrations of N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine were administered orally to Chung model rats. A model in accordance with Kim and Chung

1992, Pain 150, pp 355-363 (*Chung* model), for chronic pain (in particular peripheral neuropathy) involves the surgical ligation of the L5 (and optionally the L6) spinal nerves on one side in experimental animals. Rats recovering from the surgery gain weight and display a level of general activity similar to that of normal rats. However, these rats develop abnormalities of the foot, wherein the hindpaw is moderately everted and the toes are held together. More importantly, the hindpaw on the side affected by the surgery appears to become sensitive to pain from low-threshold mechanical stimuli, such as that producing a faint sensation of touch in a human, within about 1 week following surgery. This sensitivity to normally non-painful touch is called "tactile allodynia" and lasts for at least two months. The response includes lifting the affected hindpaw to escape from the stimulus, licking the paw and holding it in the air for many seconds. None of these responses is normally seen in the control group.

**[0055]** Rats are anesthetized before surgery. The surgical site is shaved and prepared either with betadine or Novacaine. Incision is made from the thoracic vertebra XIII down toward the sacrum. Muscle tissue is separated from the spinal vertebra (left side) at the L4 - S2 levels. The L6 vertebra is located and the transverse process is carefully removed with a small rongeur to expose the L4 - L6 spinal nerves. The L5 and L6 spinal nerves are isolated and tightly ligated with 6-0 silk thread. The same procedure is done on the right side as a control, except no ligation of the spinal nerves is performed.

**[0056]** A complete hemostasis is confirmed, then the wounds are sutured. A small amount of antibiotic ointment is applied to the incised area, and the rat is transferred to the recovery plastic cage under a regulated heat-temperature lamp. On the day of the experiment, at least seven days after the surgery, typically six rats per test group are administered the test drugs by intraperitoneal (i.p.) injection or oral gavage. For i.p. injection, the compounds are formulated in d $H_2O$ and given in a volume of 1 ml/kg body weight using an 18-gauge, 3 inch gavage needle that is slowly inserted through the esophagus into the stomach.

**[0057]** Tactile allodynia is measured prior to and 30 minutes after drug administration using von Frey hairs that are a series of fine hairs with incremental differences in stiffness. Rats are placed in a plastic cage with a wire mesh bottom and allowed to acclimate for approximately 30 minutes. The von Frey hairs are applied perpendicularly through the mesh to the mid-plantar region of the rats' hindpaw with sufficient force to cause slight buckling and held for 6-8 seconds. The applied force has been calculated to range from 0.41 to 15.1 grams. If the paw is sharply withdrawn, it is considered a positive response. A normal animal will not respond to stimuli in this range, but a surgically ligated paw will be withdrawn in response to a 1-2 gram hair. The 50% paw withdrawal threshold is determined using the method of Dixon, W.J., Ann. Rev. Pharmacol. Toxicol. 20:441-462 (1980) hereby incorporated by reference. The post-drug threshold is compared to the pre-drug threshold and the percent reversal of tactile sensitivity is calculated based on a normal threshold of 15.1 grams.

**[0058]** Table 2 below shows the peak allodynia reversal at 30 µg/kg, 100 µg/kg or 300 µg/kg doses.

**Table 2**

| Dose | Peak Allodynia Reversal (Oral, 30 min.) |
|---|---|
| 300 µg/kg | 84% +/- 7.5% |
| 100 µg/kg | 68% +/- 12.7% |
| 30 µg/kg | 28% +/- 9.5% |

**[0059]** As shown in Table 2, 30 µg/kg oral dosage resulted in 28% allodynia reversal. The analgesic effect was seen quickly, in about 30 minutes. Fig. 1 shows a peak percent allodynia reversal at 30 minutes followed by a steady decrease to baseline at about 120 minutes.

**Example 7**

***In Vivo* Activity Data**

**[0060]** Data was acquired from wild type rats administered N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine intraperitoneally (IP). Rats were split into groups of six and administered 1 mg/kg or 10 mg/kg doses of N-(2,3-dichlorobenzyl)-4,5-dihydro-1H-imidazol-2-amine to assess the sedative effects of the administration of the agent. As can be seen in both Fig. 2 and Table 3, 10 mg/kg had a significant sedative effect on the dosed rats.

**Table 3**

| Dose | Sedative Effect (IP) |
|---|---|
| 1 mg/kg | No significant effect |
| 10 mg/kg | 23% sedating |

**[0061]** The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

**[0062]** Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted

from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

**[0063]** Certain embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description.

# REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

**Patent documents cited in the description**

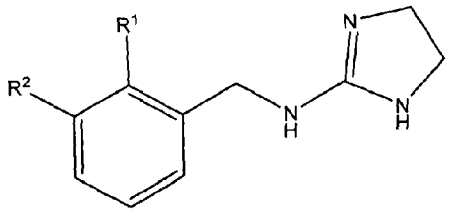

- WO2009052075A [0006]


**Non-patent literature cited in the description**


- **DAVID J. H. et al.**J. Org. Chem., 1983, vol. 48, 289-294 [0032]
- **MESSIER et al.**Pharmacol. Toxicol., 1995, vol. 76, 308-311 [0053]
- **KIMCHUNG**Pain, 1992, vol. 150, 355-363 [0054]
- **DIXON, W.J.**Ann. Rev. Pharmacol. Toxicol., 1980, vol. 20, 441-462 [0057]

**Patentkrav**

**1.** Forbindelse repræsenteret af den følgende formel, eller et farmaceutisk acceptabelt salt eller tautomer deraf, til anvendelse i en fremgangsmåde til behandling af en tilstand eller sygdom hos et pattedyr valgt fra hypertension, hjertesvigt, astma, depression, glaukom, forhøjet intraokulært tryk, iskæmisk neuropati, optisk neuropati, smerte, en nethinde-degenerativ tilstand, slagtilfælde, en kognitiv defekt, en neuropsykiatrisk tilstand, stofafhængighed, stofmisbrug, abstinenssymptomer, OCD, fedme, insulinresistens, en stress-relateret tilstand, diarré , diurese, nasal forstoppelse, ADD (attention deficit disorder), psykose, angst, autoimmune sygdom, Crohns sygdom, gastritis, og en neurodegenerativ sygdom:




hvor $R^1$ og $R^2$ er uafhængigt valgt fra halogen og $C_{1-4}$ halogeneret alkyl.

**2.** Forbindelse eller et farmaceutisk acceptabelt salt eller tautomer deraf til anvendelse ifølge krav 1, hvilken er en af de følgende forbindelser eller et farmaceutisk acceptabelt salt eller tautomer deraf:

N-(2-chlor-3-fluor-benzyl)-4,5-dihydro-1H-imidazol-2-amin,

N-(2-fluor-3-trifluormethyl-benzyl)-4,5-dihydro-1H-imidazol-2-amin,

N-(2-fluor-3-chlor-benzyl)-4,5-dihydro-1H-imidazol-2-amin,

N-(2,3-dichlorbenzyl)-4,5-dihydro-1H-imidazol-2-amin,

N-(2-chlor-3-brom-benzyl)-4,5-dihydro-1H-imidazol-2-amin, og

N-(2-brom-3-chlor-benzyl)-4,5-dihydro-1H-imidazol-2-amin.

**3.** Forbindelse eller et farmaceutisk acceptabelt salt eller tautomer deraf til anvendelse ifølge krav 2, hvilken er N-(2,3-dichlorbenzyl)-4,5-dihydro-1H-imidazol-2-amin eller et farmaceutisk acceptabelt salt eller tautomer deraf.

**4.** Forbindelse eller et farmaceutisk acceptabelt salt eller tautomer deraf til anvendelse ifølge et hvilket som helst foregående krav, hvor tilstanden eller sygdommen er smerte.

**5.** Forbindelse eller et farmaceutisk acceptabelt salt eller tautomer deraf til anvendelse ifølge krav 4, hvor smerten er valgt fra visceral smerte, hornhindesmerte, hovedpinesmerte, migræne, kræftsmerte, rygsmerte, irritabel tyktarmssmerte, muskelsmerte, og smerte associeret med diabetisk neuropati.

# DRAWINGS

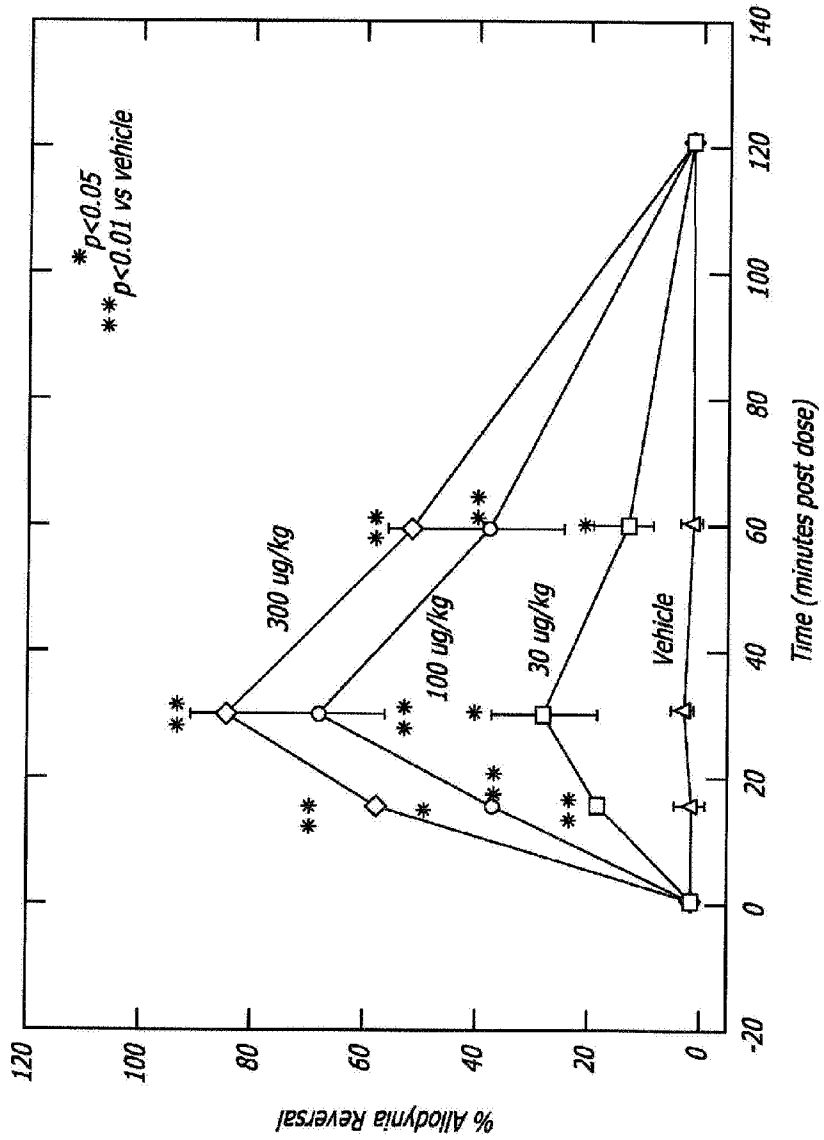



FIG. 1

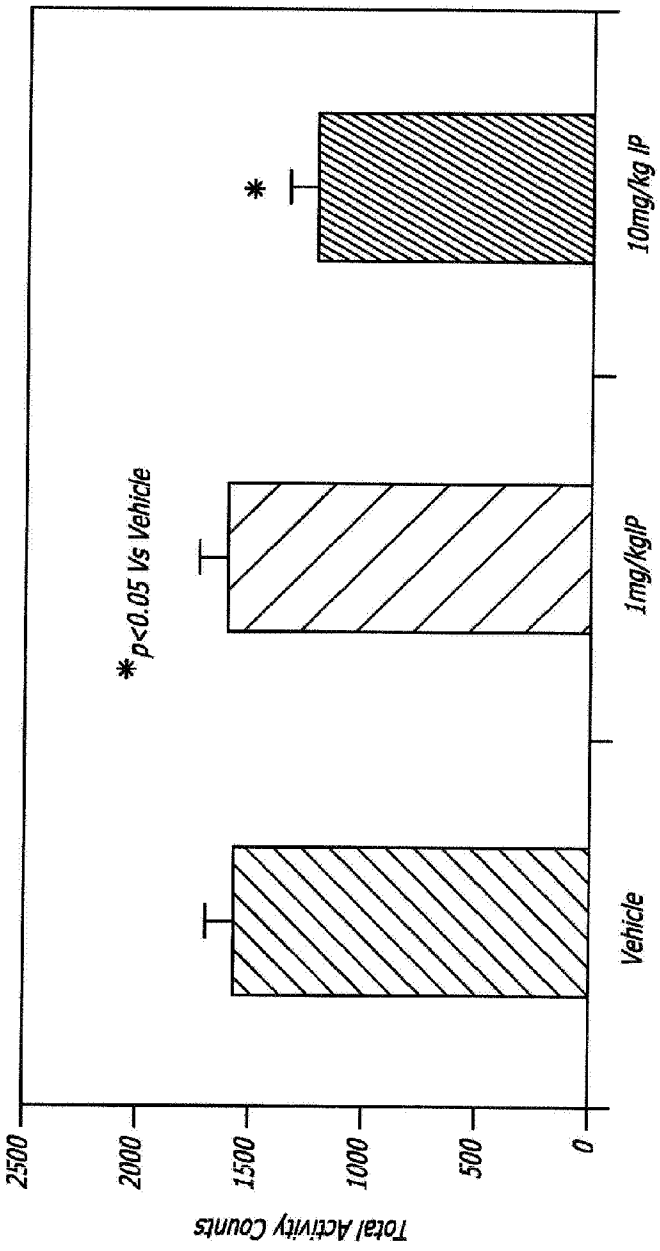

Total Activity Counts
2500
2000
1500
1000
500
0
*p<0.05 Vs Vehicle
*
Vehicle
1mg/kg IP
10mg/kg IP

FIG. 2